Beyond the Fat Boy: the intertwining pathophysiology of sleep apnea

Over the past 20 years, increasing data have accumulated underscoring the public health importance of sleep apnea with growing evidence of its high prevalence and myriad clinical manifestations. This condition, rarely diagnosed in the past, had been considered to occur predominantly as a manifestation of morbid obesity and considered to affect almost exclusively middle-aged men. Sleepiness and cor pulmonale were the most commonly recognized consequences, with many other comorbidities, such as hypertension and diabetes, considered to be related to the confounding effects of obesity. Early studies focused on mechanisms by which excessive fat compromised lung mechanics and upper airway patency, including its structure and propensity for collapse. Likewise, much of the literature, including articles in the Journal of Applied Physiology, initially examined the role of discrete sets of muscles that influenced airway size and function and the roles of chemoreflexes and proprioception leading to apnea propensity. However, an explosion of research that has included elegant physiological studies of humans and animals, studies of genetically altered rodents, and large-scale epidemiological studies have revolutionized approaches to sleep apnea research. Indeed, the study of sleep apnea pathophysiology is no longer strictly in the domain of the respiratory physiologist, but it requires the active collaboration of investigators with expertise in genetics, cardiovascular physiology, endocrinology, and other disciplines. Indeed, clinical and epidemiological data showing strong associations of sleep apnea with components of the metabolic syndrome (diabetes, visceral obesity, hyperlipidemia, and hypertension) point to the complexity of its pathophysiological basis and expression.

In this mini-series, the intertwining pathophysiology of sleep apnea is addressed from several perspectives. In the October issue, Young, Peppard, and Taheri in an article entitled “Excess weight and sleep-disordered breathing” provide solid data that define the prevalence of sleep apnea across population subgroups. They report that mild or worse sleep apnea may occur in 17% of the adult United States population, with almost 6% suffering from moderate to severe disease. The authors present new analyses that attempt to estimate the extent to which this disease burden is attributable to excessive weight. Their estimates not only underscore the importance of excessive weight as the major risk factor for sleep apnea but also provide data that identify the importance of a variety of other host characteristics that may interact with weight to alter susceptibility to sleep apnea. Noteworthy, although sleep apnea occurs in substantial numbers of females, a number of studies indicate that at any given weight, sleep apnea is more prevalent, and possibly more progressive, in males, suggesting roles for sex hormones or other hormonal influences that modify the expression of this disease. Additionally, new data from Asia, from both developed and developing countries where obesity levels are lower than in the United States, indicate that high proportions of those populations may suffer from sleep apnea. Interesting, cross-country/cross-ethnic comparisons indicate that although mean levels of weight vary across populations, the overall impact of an elevation of weight relative to the mean in each population confers similar increased risk for sleep apnea. The latter highlight the importance of other ethnic or cultural differences that operate across populations to modify sleep apnea risk profiles. In this light, Patel, also in the October issue, critically examines the genetic basis for sleep apnea in an article “Shared genetic risk factors for obstructive sleep apnea and obesity,” and shows data that clearly support its significant genetic underpinnings. Importantly, he does not trivialize the role of obesity genes in this disorder. Rather, he describes the complexity of genes that may operate through disparate pathways, including those that influence obesity as well as those that operate independently of obesity genes. Specifically, his analyses indicate that ~50% of the genetic variance for sleep apnea can be attributed to genes apart from those that determine body mass index. He explores the potential importance of genes that influence ventilatory control, upper airway anatomy, and metabolism as intermediate traits important in understanding the pathogenesis of sleep apnea. However, Patel also identifies the importance of understanding genes with pleiotropic effects, i.e., that influence the expression of both obesity and sleep apnea. This review also discusses the relevance to studies of sleep apnea of gene-environmental interactions (how exposures to sleep apnea stresses may alter gene expression.) For example, genes for diabetes that may be differentially expressed in backgrounds of hypoxemia may be optimally studied in subjects who are regularly exposed to sleep apnea-related hypoxemia.

Among the more recently identified comorbidities of sleep apnea are diabetes and insulin resistance—public health problems growing at epidemic rates. Although diabetes had been recognized for some time to be associated with sleep apnea, much of the early literature attributed these associations to obesity, a common factor to both conditions. In the November issue of this journal, insulin resistance is addressed as it relates primarily to sleep apnea-related stresses in an article entitled “Disorders of glucose metabolism in sleep apnea” by Punjabi and Polotsky. In a companion review entitled “Sleep loss: a novel risk factor for insulin resistance and Type 2 diabetes” by Spiegel et al., insulin resistance is also explored more broadly, with an emphasis on the role of sleep fragmentation and sleep deprivation on altering indexes of metabolic control. The authors summarize exciting theories derived from a congruence of animal and human experimental and epidemiological data indicating that both chronic intermittent hypoxemia and sleep deprivation cause a wide range of systemic inflammatory and hormonal responses involving the adipocyte, the hypothalamic-pituitary-adrenal axis, and sympathetic nervous system. The data summarized in these two reviews provide elegant pathophysiological mechanisms that suggest novel etiological mechanisms that relate sleep disorders to a variety of chronic diseases. Furthermore, relating these data to those reviewed by Patel on the shared genetic bases for sleep apnea and obesity raises the possibility that diabetes and sleep apnea are linked by both causal as well as common genetic mechanisms.
In the final issue of this series, Caples, Wolk, and Sommers describe the interactions of cardiac function and obstructive and central sleep apnea in “Influence of cardiac function and failure on sleep-disordered breathing.” The importance of considering the interactive, and bidirectional, associations between cardiac function and sleep-disordered breathing is explored. These disorders may be linked by abnormalities in lung mechanics, ventilatory control, circulation time, and sympathetic nervous system activation; additionally, the authors speculate on the intriguing possibility that abnormalities in leptin metabolism due to heart failure may impact hypercapnic ventilatory responses and apnea propensity. This speculation further implicates close interactions of metabolic phenotypes with sleep-cardiorespiratory traits. Finally, Bradley and Ryan provide an overview of the pathogenesis of obstructive sleep apnea. This review identified fundamental mechanisms that influence airway propensity and explores the interaction among a number of risk factors.

It is the hope that the readers of the Journal of Applied Physiology will find this mini-series stimulating, further encouraging sleep apnea research that includes consideration of overlapping pathogenetic pathways. The aggregate work presented suggests the importance of considering how hormonal and cardiovascular interactions influence propensity for sleep apnea, and, conversely, how sleep apnea contributes to a wide range of physiological disturbances that impact common chronic diseases. Exciting data are accumulating that indicate the complexity of the sleep apnea phenotype, far exceeding the caricature suggested by Charles Dickens’s “Fat Boy” in The Pickwick Papers. Further understanding this phenotype will likely lead to progress in understanding fundamental physiological mechanisms, as well as lead to developing improved disease prevention and treatment strategies. This work is, however, largely in its infancy. As the reviews included in this mini-series indicate, additional research is need to fully understand such factors as the physiological and molecular bases for sex differences in sleep apnea and the genetic origins and relative importance of specific intermediate phenotypes in the pathogenesis of sleep apnea. Consideration of the intertwining pathophysiologies of sleep apnea will complicate disease models that are based on simple, unidirectional causal arrows. More likely, arrows will extend bidirectionally and circularly. Although evidence that sleep disturbances may promote cardiovascular disease and diabetes is striking, it is also likely that there is a high risk group of people who are genetically at risk for several related disorders. The ultimate test, and population need, will be to determine whether interventions aimed at treating sleep apnea and/or improving sleep quality and increasing sleep duration will reduce the health burden of chronic diseases such as hypertension, diabetes, and heart failure.

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